Featured Article

Long-Term Analysis and Prospective Validation of a Prognostic Model for Patients with High-Risk Primary Breast Cancer Receiving High-Dose Chemotherapy

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ABSTRACT

Purpose: We described previously a prognostic model for high-risk primary breast cancer patients receiving high-dose chemotherapy (HDC). Such model included nodal ratio (no. involved nodes:no. dissected nodes), tumor size, hormone receptors, and HER2. In the present study we intended to test this model prospectively in a second patient cohort. In addition, we analyzed the long-term overall outcome of our HDC trials.

Experimental Design: We analyzed all 264 patients enrolled since 1990 in our prospective trials for 4–9+ nodes, or inflammatory disease. Patients of the second cohort (treated since 1997) had their prognostic score estimated prospectively before receiving HDC.

Results: Fourteen patients (5.3%) died from HDC-related complications. At median follow-up of 7.1 years, relapse-free survival and overall survival of the whole group were 69.8% and 73%, respectively. Median time to relapse was 14 months (63.5% relapses within the first 2 years, 6.7% after year 5). The model was validated in the second cohort, establishing the following pretransplant risk categories: low risk (low score, HER2–), 44% patients, 87% freedom from relapse (FFR); intermediate risk (low score, HER2+), 29% patients, 68% FFR; and high risk (high score, any HER2), 27% patients, 49% FFR.

Conclusions: Few relapses are seen after year 5 of follow-up, which indicates the need for mature results of the randomized trials before their final interpretation or meta-analysis. Our prospectively validated prognostic model, if additionally confirmed in the randomized trial populations, may provide an insight into the relative benefit of HDC in different risk patient subsets.

INTRODUCTION

The prognosis of patients with high-risk primary breast cancer (HRPBC), defined by extensive axillary involvement (≥4+ axillary lymph nodes) or inflammatory breast carcinoma (IBC), is poor. Long-term relapse-free survival (RFS) rates are <50% after multimodal postoperative treatment including standard-dose chemotherapy (SDC). Their outcome does not appear significantly improved with the recent incorporation of taxanes into the adjuvant armamentarium. Whereas randomized trials testing the addition of paclitaxel or docetaxel to adjuvant SDC have shown benefit in the overall group of node-positive patients, these agents seem to have little or no impact on patients with high-risk disease (1, 2).

Peters et al. (3) at Duke University pioneered the evaluation of high-dose chemotherapy (HDC) for HRPBC. Their encouraging early results using cyclophosphamide/cisplatin/1,3-bis(2-chloroethyl)-1-nitosourea (STAMP-I) in patients with ≥10+ nodes, as well as those from other groups in that and other high-risk populations, prompted numerous worldwide randomized Phase III studies comparing HDC with SDC, which have completed accrual (4–12). Outcome of the control arms appears better than expected, with no significant differences detected in most, but not all, trials. However, follow-up duration is, in most cases, still limited, and their results cannot be considered conclusive at this point.

Whereas many investigators have reported the short-term results of their HDC trials in HRPBC, little is known about long-term outcome of these patients after transplant. An update of the Duke Phase II trial of STAMP-I in 85 patients with ≥10+ nodes showed 60% RFS and 63% overall survival (OS) rates at median FU of 11 years (13). Damon et al. (14) reported 53% RFS and 65% OS rates at median FU of 6.9 years in 80 patients with ≥10+ nodes treated with high-dose cyclophosphamide/thiotepa/mitoxantrone. The actuarial 7-year RFS and OS rates of 114 HRPBC patients treated at City of Hope (Duarte, CA) with two different HDC regimens were 43% and 57%, respectively (15).

Knowledge of the long-term natural history of HRPBC patients treated with HDC in Phase II trials will help interpret the results of the randomized studies, and suggest areas of strength and weakness of the reported results. It is possible that specific subsets of high-risk patients may benefit from HDC, as currently administered and tested in the randomized trials, as opposed to the entire HRPBC population. In this regard, validated prognostic factors or models might aid in selection of patient groups that would be candidates for future HDC-based research.

We present the long-term analysis of patients enrolled in...
prospective studies of HDC at the University of Colorado, as well as the prospective validation of our previously described prognostic models in this population.

PATIENTS AND METHODS

Patient Population. We evaluated all 264 patients enrolled in prospective research trials of HDC for HRPBC at the University of Colorado Bone Marrow Transplant Program between 1990 and 2001 (Table 1). These trials included Phase II and III studies for populations with 4–9+ axillary nodes (n = 93; Ref. 16), ≥10+ nodes (n = 120; Ref. 17), or inflammatory breast carcinoma (IBC; n = 51; Ref. 18). These studies were approved by the University of Colorado Cancer Center Protocol Review Committee and the Institutional Review Board. All of the patients gave written informed consent before study entry. Protocols required adequate visceral organ function, as described previously (16–18). Our policy throughout the years has been to enroll all of the patients who met eligibility criteria, consented to the treatment, and whose insurance agreed to pay for the proposed treatment. Patients received HDC within 6 months of primary definitive surgery (mastectomy or lumpectomy with negative margins). IBC patients received preoperative chemotherapy, followed by surgery and HDC. Non-IBC patients received four cycles of Adriamycin-containing chemotherapy before HDC. Absence of relapse during pretransplant SDC was a requirement for these trials. Pretransplant staging tests were computed tomography scans of the head, chest, abdomen, and pelvis, bone scan, and bilateral bone marrow biopsies. After mobilization with granulocyte colony-stimulating factor, collection, and cryopreservation of hematopoietic progenitor cells, patients received HDC with cyclophosphamide (5625 mg/m²), cisplatin (165 mg/m²), and 1,3-bis(2-chloroethyl)-1-nitrosourea (600 mg/m²; STAMP-I regimen), as described previously. Subsequently, unselected hematopoietic progenitor cells were infused, and granulocyte colony-stimulating factor was administered at 5 μg/kg/day until neutrophil recovery. Thirty-nine patients enrolled in the Phase II 4–9+ positive node trial who received 1,3-bis(2-chloroethyl)-1-nitrosourea at 450 mg/m² presented no significantly different 1,3-bis(2-chloroethyl)-1-nitrosourea pharmacokinetic exposure than the other 225 patients receiving 600 mg/m² (16).

Post-transplant treatment included locoregional radiotherapy upon platelet recovery. Tamoxifen was prescribed for 5 years to patients with estrogen receptor/progesterone receptor (ER/PR)-positive tumors.

Prognostic Analysis. We reported previously the analysis of 174 patients treated through July 1997 at median FU of 3.75 (1–7) years (17). That subset constitutes cohort “A” of the current analysis. In that study the following variables were identified as independent predictors of outcome: (a) pathological tumor size; (b) ER/PR; and (c) nodal ratio (no. positive axillary nodes/no. dissected nodes). We developed the following scoring system from the logistic regression model containing those three independent variables:

\[ \text{Score} = (\text{nodal ratio} \times 3.05) + (\text{tumor size} \times 0.15) - \left( \frac{\text{ER/PR}}{1.15} \right) \]

In this formula, size is entered in cm, and ER/PR is assigned “0” if negative (both ER and PR negative) and “1” if positive (ER and/or PR positive). A cutoff score of 2.41 provided the model with the best sensitivity and specificity. Thus, patients with low (<2.41) and high (≥2.41) scores before transplant presented highly statistically significant differences in RFS and OS. This model was validated in an external sample of 225 HRPBC patients treated at Duke University with STAMP-I and followed for a median 3.8 (0.3–10.6) years (17).

In a subsequent study, immunohistochemical analysis of tumor blocks retrospectively collected from 146 patients allowed us to identify an independent adverse prognostic value for HER2 overexpression (19).

The present report constitutes the expansion and validation of our prior studies. We calculated in a prospective fashion, at the time of accrual before HDC, the clinical score of all patients enrolled in our studies since July 1997. These patients constitute cohort “B” of the current study. In this report we describe the following: (a) long-term outcome analysis of our entire HRPBC population; (b) FU analysis of cohort “A”; (c) prospective prognostic evaluation of cohort “B”; and (d) mature evaluation of HER2, expanding its analysis to 231 patients.

Immunohistochemical HER2 Analyses. Paraffin-embedded tumor blocks were obtained from the referring institutions. We used the monoclonal antibody CB-11 (Vantana, Tucson, AZ) as described previously (19). Prior studies had shown 100% specificity for this antibody when compared with techniques measuring DNA amplification (20). The sensitivity of our assay was maximized through the techniques of epitope retrieval and avidin-biotin binding. The scoring criteria were as follows: 0% stained cells = 0; 1–33% = 1+; 34–66% = 2+;
RESULTS

Description of Outcome in the Whole Group (n = 264). At median follow-up of 7.1 (1.5–11) years, the RFS and OS rates of the overall group of 264 patients are 69.8% and 73%, respectively (Fig. 1). The RFS and OS rates in the different populations were as follows: 4–9+ nodes, 72% and 75.2%, respectively; ≥10+ nodes, 64.1% and 65.8%, respectively; and IBC, 64.7% and 70.5%, respectively. Median RFS or OS times have not been reached for the overall population or for any group. There were no significant differences in RFS (P = 0.39) or OS (P = 0.36) among the three groups (P = 0.3; Fig. 2A). The differences in RFS (P = 0.21) or OS (P = 0.14) between patients with 4–9+ and ≥10+ nodes did not reach significance. Likewise, no significant differences were noted after comparing RFS (P = 0.58) or OS (P = 0.89) between patients with non-IBC (4–9+ and ≥10+ node groups combined) and those with IBC (Fig. 2B).

Fourteen patients (5.2%) died from early treatment-related complications within the first 3 months post-transplant, 4 of 93 in the 4–9+ node group, 8 of 120 in the ≥10+ node group, and 2 of 51 among IBC patients. Causes of death were acute lung injury (n = 6), venoocclusive disease of the liver (n = 3), hemolytic-uremic syndrome (n = 2), sepsis (n = 2), and acute cardiomyopathy (n = 1). They were considered events in the overall outcome analyses (RFS and OS; Fig. 1 and Fig. 2, A and B), but were excluded from the prognostic analyses (FFR and OS).

Statistical Methods. Correlations between categorical and continuous variables were assessed using the χ² or the Fisher’s exact test, and Student’s t test, respectively. Median FU times were estimated among surviving patients. RFS was defined as the time from study entry to documented relapse or to death without relapse. OS was defined as the time from study entry to death from any cause. FFR curves, plotted in the prognostic studies but not in the descriptive overall outcome analyses, excluded 14 patients who died from early treatment-related complications, as they did not offer meaningful information regarding risk of relapse. In the FFR curves, patients who died from late secondary malignancy (n = 3) or from an unrelated event (n = 1), with no evidence of breast cancer at the time of their deaths or at latest follow-up, were censored as free of breast cancer at those times. All of the survival times were analyzed using the Kaplan-Meier method (21). The log-rank test was used to study the correlation of potential prognostic variables with survival times (22). Multivariable analyses of FFR and OS used proportional hazard Cox regression models (23). The significance of the models was evaluated with the likelihood ratio test. Individual coefficients were tested using the Wald test. The proportionality assumption for the variables was assessed with Kaplan-Meier curves. All of the Ps presented are two-tailed.

Fig. 1 Overall survival (OS) and relapse-free survival (RFS) in the overall high-risk primary breast cancer population (n = 264).

Fig. 2 Relapse-free survival (RFS) per protocol. A, RFS in the 4–9+ node (○, n = 93), ≥10+ node (+, n = 120), and inflammatory breast carcinoma (IBC) groups (▲, n = 51; P = 0.39). Comparison between the 4–9+ and ≥10+ groups, P = 0.21. B, RFS of non-IBC (4–9+ and ≥10+ groups combined, n = 213) and IBC groups (P = 0.58).
Two patients in the original 4–9+ node Phase II study and 1 patient in the ≥10+ node study developed secondary acute myelogenous leukemia at 5 and 6 years after HDC. All 3 died from complications related to salvage transplant (allogeneic in the first 2 and autologous in the third case). No breast cancer was identified in their postmortem exams. They were considered events in the descriptive outcome analyses (Fig. 1 and Fig. 2, A and B), but were censored as free of breast cancer at the time of death for the purpose of prognostic analyses (see Figs. 4–8).

One IBC patient died in a car accident shortly after her 3-year FU visit, at which time she had been noted to be disease free. Similar to the 3 patients with secondary AML, she was considered an event in the outcome analyses and was censored as disease free at 3 years for purpose of the prognostic analyses.

Seventy-two patients experienced tumor relapse at a median 14 (1–75) months after HDC. The incidence of relapses decreased significantly with time ($P < 10^{-5}$; Fig. 3). Sixty-four percent of all relapses occurred within the first 2 years of follow-up, and only 6% after year 5. The median survival after recurrence was 7 (range, 1–81) months.

**Prognostic Analyses of the Clinical Score.** In the overall group ($n = 264$), 74% patients had a low score and 26% had a high score. The distribution of low and high scores was not uniform across the three subgroups, with significantly fewer patients with 4–9+ nodes having a high score than in the ≥10+ node or IBC subgroups, 9%, 36%, and 33%, respectively ($P < 0.001$).

The scoring system is applicable to both the IBC and non-IBC populations (Fig. 4). The differences between low-score non-IBC and IBC patients ($P = 0.9$), or between high-score non-IBC and IBC patients ($P = 0.3$) were not significant.

At median follow-up of cohort A ($n = 174$) of 8 (5–11) years, there persists a statistically significant and large difference in FFR ($P = 0.0001$; Fig. 5A) and OS ($P < 0.001$) between patients with low and high scores. Patients with a low score (74% of the sample) experienced 76.7% FFR and 79% OS rates. The FFR and OS rates among high-score patients (26% of this cohort) were 49% and 51%, respectively.

Cohort B ($n = 76$) has been followed for a median 3 (1.5–6) years. The distribution of patients with low and high scores is the same as in cohort A (74% and 26%, respectively).

There are significant differences in FFR (86% and 58%, respectively, $P = 0.007$; Fig. 5B) and OS (90% and 58%, respectively; $P = 0.0002$) between patients with low and high clinical scores. In the overall group of 250 patients who were evaluable for the prognostic analyses (cohorts A + B), the differences between patients with low and high scores were highly statistically significant in FFR (79.5% and 44.5%, respectively; $P < 0.00001$) or OS (83% and 46%, respectively; $P < 0.00001$).

**Prognostic Evaluation of HER2.** HER2 status was evaluated in 231 patients, followed for a median 7 (1.5–11) years. HER2 overexpression was detected in 43% of the patients. HER2− and HER2+ patients had statistically significant differences in FFR (78% and 61%, respectively; $P = 0.001$; Fig. 6A) and OS (81% and 67%, respectively; $P = 0.009$; Fig. 6B).

**Combined Model Including Clinical Score and HER2.** Long-term multivariate analyses showed maintained independent value of nodal ratio, tumor size, ER/PR, and HER2 for FFR and OS (Table 2). As expected, models that included the combined clinical score (as a single variable) and HER2 showed an independent value for both (data not shown).

Combining the clinical score with HER2 establishes four categories: (a) low score, HER2−; (b) low score, HER2+; (c) high score, HER2−; and (d) high score, HER2+ (Fig. 7). The differences between HER2− and HER2+ patients within the low-score subgroup reached statistical significance for FFR ($P = 0.001$) and OS ($P = 0.004$). In contrast, HER2 did not have a significant impact on FFR ($P = 0.8$) or OS ($P = 0.6$) among patients with a high score. Thus, our model remains significant after long-term validation, with the following risk categories ($P < 10^{-5}$): low risk, low score, $HER2- (44%$ patients, $87%$ FFR, and $89%$ OS rates); intermediate risk, low score, HER2+ (29% patients, 68% FFR, and 71% OS); and high risk of relapse, high score, any HER2 (27% patients, 49% FFR, and 54% OS; Fig. 8, A and B).

**DISCUSSION**

At median and lead FU of 7 and 11 years, respectively, the overall RFS and OS rates of 264 HRPBC patients enrolled in our prospective Phase II HDC trials with STAMP-1 are 67% and 70%, respectively. Our data are consistent with previous long-
term reports (13–15) and suggest that the activity of HDC in HRPBC is sustained over time.

In a prior report we described a prognostic score constructed upon three independent clinical predictors of outcome in HRPBC patients receiving STAMP-I, tumor size, ER/PR status, and nodal ratio (17). The first two had a well-established prognostic role in the breast cancer literature. In a previous prognostic analysis of their HDC experience, Somlo et al. (24) had observed an independent predictive value for PR in 114 patients treated with two different high-dose combinations at City of Hope. In contrast, the nodal ratio, as defined in our previous report, constituted a novel predictor. This was in contrast to the lack of a significant predictive value of the number of involved nodes alone in our analysis. These observations were subsequently confirmed by others in their analyses of HRPBC populations treated with HDC (25–27). Recent reports of patients receiving adjuvant SDC also indicate the emerging importance of the nodal ratio, the number of uninvolved nodes, or the total number of dissected nodes (28–35). With limited axillary dissections gaining popularity among surgeons, the nodal ratio, which adjusts for the number of sampled nodes, may prove a more useful prognostic tool than the absolute number of involved nodes.

Our clinical prognostic score has undergone double validation, previously in an external independent sample, (17) and now in a prospective fashion. The score is applicable to all of the HRPBC patients who undergo surgery before HDC, either with IBC (receiving neoadjuvant chemotherapy) or without IBC. Importantly, IBC patients can be downstaged after preoperative chemotherapy, affecting the tumor size and nodal ratio. However, our model is applicable to these patients, as shown in our previous report and confirmed in the current study. Thus, we can

![Fig. 5](image1)

**Fig. 5** Prospective validation of the clinical score. A, freedom from relapse of sample “A” (original sample, n = 174) at median follow-up of 8 years. Fig. B, freedom from relapse of sample “B” (validation sample, n = 76) at median follow-up of 3 years.

![Fig. 6](image2)

**Fig. 6** Outcome according to HER2 status (n = 231). A, freedom from relapse; B, overall survival.
clearly predict long-term outcome of HRPBC patients receiving HDC with STAMP-I. It would be of interest to evaluate this score in patients receiving other HDC combinations.

The three clinical variables that compose the score and identify poor-risk patients in this model are likely to be surrogate variables for intrinsic molecular heterogeneity of HRPBC. One such molecular marker appears to be HER2. Bitran et al. (36) first suggested this effect in a small study of 25 patients. Subsequently, we and others confirmed the important value of HER2 in HDC-treated HRPPC (19, 37) or MBC patients (38–41). The current long-term multivariate analysis of our large collection of tumor blocks of HRPBC patients receiving homogeneous HDC provides strong evidence of a major independent prognostic value of HER2 in this setting.

The overall question of the value of HDC for patients with HRPBC is subject of intense controversy. At least 15 randomized trials, 10 of them enrolling >300 patients, have compared diverse forms of HDC to lower doses of chemotherapy (42). Their results, in most cases preliminary, appear contradictory at this point (Table 3). There are clearly negative trials after fairly mature FU, such as those conducted by the Cancer and Leukemia Group B, (4) Eastern Cooperative Oncology Group, (5) or the Scandinavian Breast Cancer Group (6). In contrast, some studies, such as the French Pégase 01 (7) and the trial conducted by the West German Study Group (8), indicate superiority of transplant at the time of their first analysis. Some other trials show a nonsignificant trend in favor of transplant, like the National Dutch (9) and the International Breast Cancer Study Group trials (10). Finally, there are trials that show no significant differences in all of the accrued patients, but do suggest a possible benefit from HDC among those patients with longest FU, such as the Anglo-Celtic (11) and the German Autologous Bone Marrow Group studies (12).

The length of FU is critical in the interpretation of the randomized trials, as RFS and OS of HRPBC patients may differ after SDC and HDC. Median time to relapse of patients who receive conventional treatment is 30 months (43). These relaps-
Table 3  Randomized trials of HDC* in HRPBC enrolling more than 300 patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population (# + nodes)</th>
<th>Median FU (yrs)</th>
<th>% RFS</th>
<th>% OS</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>HDC</td>
<td>Control</td>
</tr>
<tr>
<td>Netherlands⁹</td>
<td>≥10</td>
<td>885</td>
<td>4.75</td>
<td>65</td>
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<td>CALGB³</td>
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</tr>
<tr>
<td>ECOG³</td>
<td>≥10</td>
<td>540</td>
<td>6.1</td>
<td>55</td>
</tr>
<tr>
<td>Scandinavia (SBCG)⁶</td>
<td>≥5 to 8</td>
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<td>5</td>
<td>47</td>
</tr>
<tr>
<td>Germany (WSG)⁶</td>
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<td>403</td>
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<td>302</td>
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<td>58</td>
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</table>

* HDC: high-dose chemotherapy; HRPBC: high-risk primary breast cancer; RFS: relapse-free survival; OS, overall survival; CALGB, Cancer and Leukemia Group B; ECOG, Eastern Collaborative Oncology Group; SBCG, Scandinavian Breast Cancer Group; WSG, West German Study Group; IBCSG, International Breast Cancer Study Group; PEGASE, Programme d’Étude de la Greffe Autologue dans les Cancers du Sein; GABG, German Autologous Bone Marrow Transplant Group; NR, not reported; NS, not significant.

...ing patients typically survive 2 years after recurrence. In contrast, median time to relapse in our HDC trials was 14 months, and median postrelapse survival was only 7 months. Thus, whereas a meta-analysis can ultimately adjust for possible lack of statistical power of the individual trials to detect small differences with some clinical relevance, adequate FU remains essential, in particular for OS comparisons.

Varying admixtures of high-risk versus low-risk patients could also explain the differences in the randomized trial results. Thus, there could be an important value of using our model to probe the various trial results for hypothesis generation. It would be important to identify those patient subsets that might benefit from HDC, as administered in the randomized trials, as well as those subpopulations that should be candidates for alternative experimental approaches. Analyses are under way evaluating our model in both arms of the Dutch randomized study.⁵

The time pattern of relapses observed in our HDC trials may reflect a highly aggressive and refractory nature of those tumors with extensive node involvement that are not eradicated by HDC. It is conceivable that patients who would relapse shortly after SDC are not affected by high-dose consolidation and would clearly need a new approach, whereas HDC could potentially be of value for those who would take longer time to relapse after SDC. It will be useful in the future to evaluate our prognostic model in patients who have been treated with SDC. Because the low-risk group comprises more than half the patients we studied (Fig. 8), it would be of particular interest to compare the outcome of these patients treated with either SDC or HDC. Retrospective comparisons of our HDC data with conventionally treated patients are under way and will be the subject of a future report. These comparisons, whereas not randomized, may generate hypotheses of how subgroups most likely to benefit from HDC might be identified and studied. Should those analyses suggest that the high-risk subgroup had similar outcomes with either SDC or HDC, it would seem appropriate to identify novel strategies to study these patients in the future.

The use of multivariate prognostic modeling to direct breast cancer protocol design is likely to become more common, as it has in studies of lymphoma and leukemia. Whereas most clinical trials studying primary breast cancer have only used hormonal status and presence of involved nodes to design treatment protocols, newer prognostic factors, such as HER2, are becoming increasingly important. In a recently reported unplanned subset analysis of the randomized Dutch trial, Rodenhuis et al. (9) noticed an apparent superiority of HDC in HER2-negative, but not HER2-positive, HRPBC patients. Whereas this observation requires additional confirmation in other randomized studies, it appears increasingly clear that HDC, as currently administered, constitutes suboptimal treatment for HER2+ patients, particularly those with other high-risk features as described by our model. The addition of anti-HER2 antibody trastuzumab to HDC may counteract the deleterious effect of HER2 overexpression. In a collaborative pilot study conducted at the University of Colorado and Duke University, we have tested the feasibility of the concurrent administration of trastuzumab with HDC to exploit their synergy (43). This trial has reached its target accrual and will be analyzed shortly. Other projects are under way to identify other molecular risk markers that could constitute novel targets in this population.

In conclusion, we have confirmed after mature FU a major prognostic value of our clinical score and of HER2 status in our series of HRPBC patients treated homogeneously with HDC. In addition, the long-term results of our prospective trials, with few relapses seen after 5 years, indicate that mature FU is required for an adequate overall interpretation or meta-analyses of the randomized trials.

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⁵ S. Rodenhuis, personal communication.
patients. Above all, we are indebted to all of our patients, who have participated in our studies throughout the years.

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